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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SAUNDERS, DAVID A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/719,045	CHAPMAN ET AL.	
	Examiner	Art Unit	
	David A. Saunders, PhD	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-15* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Amendment of 1/9/06 has been entered. Claims 1-15 are pending. Claims 1-15 are under examination. The amendment has entered no new matter.

The amendment has overcome the previously stated objection to the specification.

The following rejections of record are maintained or modified as follows:

Claims 1-10, 12-13 are 15 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Gonzales et al (6,025,158) for reasons of record.

Gonzales et al teach antibody fragments having an extended circulating half-life by virtue of being conjugated to a high m.w. polymer - e.g. PEG of 20,000 D or greater. Note especially the teaching of a "polymer molecule used to link together two antibody fragments to form a dumbbell -shaped structure." Such a "dumbbell - shaped structure" is consistent with the divalent antibody fragment of instant claim 1.

A preferred site of conjugating the polymer to the antibody fragment is at the hinge region of the latter, a most preferred site of attachment therein is a cysteine residue. See, for example, col. 19, lines 56-65. The conjugation of the polymer thereto is achieved by providing a sulfhydryl reactive moiety attached to PEG. See, for example, col. 19, Lines 35-55., col. 42, Lines 12-18,. col. 120, lines 46-52., col. 121 , Lines 59-64.

From the above claims 1-2 are anticipated or, at the least, obvious as one of numerous embodiments taught within the four corners of the reference. Teachings regarding dependent claims 3-10, 12-13 and 15 have been previously elaborated.

Applicant has urged that Gonzales et al do not describe a polymer molecule specifically linking 2 antibody Fab' fragments through a cysteine residue in the heavy chain of each fragment. The examiner notes that the exemplified Fab' fragment of Gonzales et al was engineered with a pCDNA fragment that "carries the coding sequence for the human constant IgG1 heavy domain including the free cysteine in the hinge region that was used to attach the PEG molecule." See col. 120, lines 17-36. Thus what Gonzales et al exemplified was clearly an Fab' fragment that couples to PEG via the cysteine residue of the heavy chain. Though this particularly exemplified site of coupling may not have been particularly mentioned where Gonzales et al teach the dumbbell shaped molecule, coupling Fab' to PEG via the cysteine

residue of the Fab' heavy chain is clearly within the 4 corners of the reference. At the least, one would have found it obvious to couple the later exemplified Fab' having an available cysteine residue in the hinge region of its heavy chain to PEG via the SH group of the cysteine, in order to form the dumbbell shaped structure.

Applicant has then obfuscated the issues by urging that Gonzales et al teach (col. 35, lines 53-57) a polymer derivatized with multiple functional groups permitting the attachment of two or more antibody fragments to the polymer backbone. This argument, however, ignores the clearly taught, preceding embodiment (col. 35, lines 45-47) of a polymer molecule used to link together two antibody fragments to form a dumbbell-shaped structure. Applicant further obfuscates the issues by also noting that Gonzales et al teach multiple possible linking sites within the antibody fragment that are not necessarily the cysteine of the H-chain. As noted supra, this argument ignores the clear teaching that Fab' fragments were engineered with a pCDNA fragment that "carries the coding sequence for the human constant IgG1 heavy domain including the free cysteine in the hinge region that was used to attach the PEG molecule" (col. 120, lines 17-36).

Applicant then urges that Gonzales et al teach away from the instant invention by disclosing embodiments in which the divalent F(ab')2 fragment is attached to the polymer (e.g. cols. 23-25). It is to be noted that Gonzales et al teach numerous, alternative embodiments; thus applicant cannot highlight one genre of these embodiments, while ignoring another.

Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzales et al in view of Barbanti et al (5,436,154).

Gonzales et al have been noted supra for generically teaching the bridging of Fab, Fab' or Fab'-SH antibody fragments of generic binding specificity, or more particularly of 1L-8 binding specificity, to a polymer to extend half-life of the antibody fragments. The previous rejection indicated it would have been obvious to have used the polymer coupling methods of Gonzales et al in order to extend the half-life of the anti-TNF antibodies of Barbanti et al.

Applicant has urged that there was no motivation to apply the teachings of Gonzales et al to the anti-TNF antibody fragments of Barbanti et al. First, it is to be noted that Gonzales et al

clearly teach (col. 16, lines 39-46) that the benefits of extended circulating half-life gained by conjugation to the polymer are to be expected "without regard to antigen specificity of the antibody". Further one would have been so motivated, because Gonzales et al teach that "PEGlaytion" of antibody fragments has been shown to extend serum half-life levels to useful levels; see col. 1, lines 29-32. The teaching is thus taken as indicating that antibody fragments, without regard to their antigenic specificity, do not have sufficient serum half lives in order to be therapeutically useful; there is thus a teaching of motivation by Gonzales et al to couple any antibody fragment to a polymer, such as PEG.

Second, the motivation to apply the teachings of Gonzales et al to the anti-TNF antibody fragments of Barbanti et al is implicit from the teachings of Barbanti et al. Barbanti et al teach that the anti-TNF antibodies may be used to treat numerous conditions, including those that are chronic, such as rheumatoid arthritis, AIDS, cancers, and chronic inflammatory diseases (see, for example, col. 1, lines 39-55; col. 7, lines 6-17; col. 8, lines 30-42). One would thus have reasonably been motivated to extend the half-life of anti-TNF antibody fragments, at the very least, for those situations in which there is a chronic hyperproduction of TNF, in order to obtain a more extended therapeutic effect for any single treatment.

Claim 11 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Gonzales et al do not teach conjugation of antibody fragments to a bridge of the subgenus recited in instant claim 11. Applicant has urged (response at page 7) that claim 11 should be allowed. An objected to dependent claim cannot be allowed until it is recited in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's arguments filed 1/9/06 have been fully considered but they are not persuasive for the above reasons.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is 571-272-0849. The examiner can normally be reached on Mon.-Thu. from 8:00 am to 5:30 pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Typed 3/22/06 DAS

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT 182 1644